movements associated with rhythmic movement disorder usually occur during sleep–wake transitions. Disso- ciative episodes emerge from wakefulness. Nocturnal panic attacks occur from NREM sleep, usually at the transition of stage 2 from stage 3.

Artifacts

Artifacts are commonly seen in recordings of patients with nocturnal spells and must be distinguished from epileptic activity and the EEG changes associated with parasomnias. Although artifacts may obscure the EEG, their stereotyped presentation may be supportive of the diagnosis in question. Examples of this include the EMG artifact of a tonic-clonic seizure, head or body rocking artifact in rhythmic movement disorder, and the rhythmic bilateral myoclonic artifact of bruxism. Other types of artifact that may mimic epileptiform activity include that produced by head tremor, eye movements, and tongue movements (glossokinetic artifact). Normal patterns that are occasionally misinterpreted as epileptic include posi- tive occipital sharp transients of sleep, repetitive vertex waves of young patients, small sharp spikes, wicket spikes, and rhythmic temporal theta of drowsiness.

CONCLUSIONS

VPSG combines video EEG and PSG for the evaluation of unexplained behaviors in sleep. The differential diagnosis most commonly includes epileptic seizures and parasomnias. Additional time is required for electrode placement and data analysis and more space is required on storage media. However, misdiagnosis can lead to unnecessary treatment with medications that may produce significant adverse effects and failure to make an accurate diagnosis may lead to serious, potentially fatal accidents and injuries. When VPSG fails to clarify the diagnosis, long-term video EEG monitoring should be considered.

REFERENCES


Chapter 6

Functional neuroimaging in sleep, sleep deprivation, and sleep disorders

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INTRODUCTION

The optimal management of patients with sleep disorders would require a comprehensive understanding of the underlying specific pathological mechanisms, but also an exact appreciation of the consequences of ensuing sleep disruption. The latter objective is hampered by our incomplete knowledge of normal sleep. During the last 50 years, considerable progress has been made in understanding the neural mechanisms by which sleep is induced, maintained, and regulated (McCarley et al., 1983; Barak, 1998; Kryger et al., 2000; Kryger et al., 2004; Saper et al., 2001; Steriade and Timofeev, 2004). Yet, at present, our understanding remains fragmentary and we are still striving for a comprehensive description of sleep mechanisms. Likewise, the functions of sleep are not yet undistrin- guisibly specified, although several hypotheses have been proposed (Maquet et al., 2003). Consequently, the effect of sleep on cortical and subcortical functions (Stickgold and Walker, 2007), as well as the conse- quences of sleep deprivation or fragmentation (Chee and Chua, 2008), are not yet fully understood at the different levels of description.

Neuroimaging studies conducted in sleep disorders have suffered from this fragmentary knowledge of normal sleep. For instance, they often have not been able to tease apart the pathological mechanisms of a given disorder from the consequences of the ensuing sleep disruption. Nevertheless, impressive advances have been made in some sleep disorders. In this sec- tion, our aim is to describe the present state of the art and hopefully exemplify the limitations of the available neuroimaging literature. The review begins with a short account of neuroimaging studies conducted during normal sleep, because they nicely introduce the subsequent pathological sections.

NEUROIMAGING IN NORMAL HUMANS

Introduction

Studies using positron emission tomography (PET), single photon emission computed tomography (SPECT) or functional magnetic resonance imaging (fMRI) reviewed in this section have shown that global and regional patterns of brain activity during sleep are out- standingly different from wakefulness. These studies also demonstrated the persistence of brain responses to external stimuli during sleep as well as plastic changes in brain activity related to previous waking experience.

Nonrapid eye movement (NREM) sleep

NREM sleep, when compared to wakefulness or REM sleep (Maquet et al., 1997; Maquet, 2000), is character- ized by a global decrease in cerebral blood flow (CBF), and by a regional deactivation in the dorsal pons, mesencephalon, cerebellum, thalami, basal ganglia, basal forebrain and anterior hypothalamus, prefrontal cortex, anterior cingulate cortex and precuneus. This distribution of brain activity could be at least partially explained by NREM sleep generation mechanisms in mammals (Maquet et al., 1997). Taking into account that PET measurements average cerebral activity over 90 seconds to 45 minutes, decreases in CBF and metabolism during NREM are thought to reflect a change in firing pattern, characterized by synchronized bursting activity followed by long hyperpolarization periods, more than a decrease in the average neuronal firing rate (Maquet, 2000). Accordingly, as compared to wakefulness, the average

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cerebral metabolism and blood flow levels begin to
decrease in light (stage 1 and 2) NREM sleep (Madsen
et al., 1993b; Maquet et al., 1992; Kjaer et al., 2002),
and are the lowest during deep (stage 3 and 4) NREM
sleep, also named slow-wave sleep (SWS) (Maquet
et al., 1990; Madsen et al., 1993a).
NREM sleep rhythms (spindle, delta, and slow oscil-
lations) are generated by a cascade of events occurring
in thalamocortical networks, initially induced by a
decreased activation from the brainstem tegmentum
(Steriade and Amzica, 1998). Accordingly, in humans,
brainstem blood flow is decreased during light NREM
sleep (Kajimura et al., 1999) as well as during SWS
(Braun et al., 1997; Maquet et al., 1997; Kajimura
et al., 1999; Nofzinger et al., 2002). However, during
light NREM sleep, the pontine tegmentum appears
specifically deactivated whereas the mesencephalon seems
to retain an activity that is not significantly different
from wakefulness (Kajimura et al., 1999). In SWS, both
pontine and mesencephalic segments are deactivated
(Maquet et al., 1997).
The thalamus occupies a central position in the gen-
eration of NREM sleep rhythms like spindles and delta
waves, due to the intrinsic oscillating properties of
its neurons and to the intrathalamic and thalamo-
corticothalamic connectivity. As expected, in humans,
regional CBF decreases have been found in the thalamus
during both light and deep NREM sleep (Braun et al.,
1997; Maquet et al., 1997; Kajimura et al., 1999), and also
in proportion to the power density of the electroencepha-
logram (EEG) signal in the spindle frequency range
(Hofle et al., 1997). However, in a recent study, regional
CBF was not correlated with delta activity in the thalamus
(Dung-Vu et al., 2005), suggesting the potential active
participation of the cortex in the generation of the delta
rhythm recorded on the scalp (Figure 6.1).
The role of the cortex in the generation of NREM
sleep oscillations (e.g., slow cortical rhythm) begins to

Fig. 6.1. Regional cerebral blood flow (rCBF) decrease as a function of delta power during nonrapid eye movement (NREM)
sleep.
Left panel: rCBF decreases as a function of delta power during NREM sleep. Image sections are centered on the ventro-
medial prefrontal cortex. The color scale indicates the range of Z values for the relevant voxels.
Right panel: Plot of the adjusted rCBF responses (arbitrary units) in the ventromedial prefrontal cortex in relation to the
adjusted delta power values ($\mu$V$^2$) during NREM sleep corresponding to left panel pictures: rCBF activity decreases when delta
power increases. Each circle/cross represents one scan; green circles are stage 2 scans, red crosses are stage 3–4 scans. The blue
line is the linear regression. (Reprinted from Dung-Vu et al., 2005; copyright (2005). Reprinted with permission from Elsevier.)
cerebral metabolism and blood flow levels begin to decrease in light (stage 1 and 2) NREM sleep (Madsen et al., 1991a; Maquet et al., 1992; Kjellberg et al., 2002), and are the lowest during deep (stages 3 and 4) NREM sleep, also known as slow-wave sleep (SWS) (Maquet et al., 1990; Madsen et al., 1991a).

NREM sleep rhythms (spindles, delta, and slow oscillations) are generated by a cascade of events occurring in thalamocortical networks, initially induced by a decreased activation from the brainstem tegmentum (Steriade and Amzica, 1996). Accordingly, in humans, brainstem blood flow is decreased during light NREM sleep (Kajimura et al., 1999) as well as during SWS (Braun et al., 1997; Maquet et al., 1997; Kajimura et al., 1999; Nofzinger et al., 2002). However, during light NREM sleep, the pontine tegmentum appears specifically deactivated whereas the mesencephalon seems to retain an activity that is not significantly different from wakefulness (Kajimura et al., 1999). In SWS, both pontine and mesencephalic tegmenta are deactivated (Maquet et al., 1997).

The thalamus occupies a central position in the generation of NREM sleep rhythms like spindles and delta waves, due to the intrinsic oscillating properties of its neurons and to the intrathalamic and thalamo-cortico-thalamic connectivity. As expected, in humans, regional CBF decreases have been found in the thalamus during both light and deep NREM sleep (Braun et al., 1997; Maquet et al., 1997; Kajimura et al., 1999), and also in proportion to the power density of the electroencephalogram (EEG) signal in the spindle frequency range (Hoffle et al., 1997). However, in a recent study, regional CBF was not correlated with delta activity in the thalamus (Dang-Vu et al., 2005), suggesting the potential active participation of the cortex in the generation of the delta rhythm recorded on the scalp (Figure 6.1).

The role of the cortex in the generation of NREM sleep oscillations (e.g., slow cortical rhythms) begins to be understood at the microscopic system level (Steriade et al., 1993). Their mechanisms, however, are subject to the macroscopic system levels are less well characterized. EEG power density maps have revealed a relatively typical predominance of the delta frequency band in the frontal regions whereas gamma power predominated over the vertex (Finelli et al., 2001). Human PET data similarly showed that the pattern of cortical deactivation was not homogeneously distributed throughout the cortex. As compared to wakefulness, the least active areas in SWS were observed in various associative cortices of the frontal (in particular in the dorsolateral and orbital prefrontal cortex), parietal, and to a lesser extent in the temporal and insular lobes (Braun et al., 1997; Maquet et al., 1997; Andersson et al., 1998; Kajimura et al., 1999). In contrast the primary cortices were the least deactivated cortical areas (Braun et al., 1997). A linear (inverse) relationship between delta waves and rCBF is also found in ventromedial prefrontal regions during NREM sleep (Dang-Vu et al., 2005). The reasons for this inverse association between cortical distribution remains unclear. One hypothesis is that since polymodal association cortices are the most active cerebral areas during wakefulness, and because sleep intensity is homeostatically related to prior waking activity at the regional level (Borbely, 2001), these cortices might be more profoundly influenced by SWS rhythms than primary cortices (Maquet, 2000).

The predominance of slow oscillation-related CBF decreases in ventromedial prefrontal regions may be functionally important since these cortical regions, known to deteriorate after a short sleep deprivation (Horne, 1988, 1993; Pletner and Hubert, 1996; Harrison and Horne, 1998, 1999), are involved in mood regulation and in various cognitive functions (such as planning or probability matching) (Harrison and Horne, 1999) that help in adaptation and behavior. Studies of the deleterious effects of sleep deprivation on human cognition also pointed to an exquisite sensitivity of these association cortices to sleep deprivation (see below). Recent studies have used simultaneous EEG/fMRI recordings during NREM sleep to characterize the neural correlates of NREM sleep oscillations in healthy humans. In contrast to PFT studies that described the patterns of brain activity during the different sleep stages or correlated with values of EEG spectral power, the better temporal resolution of fMRI allows assessment of the brain activity changes directly related to brief events such as spindles and delta waves. Studies have been associated with increases of brain activity in the thalamus, anterior cingulate cortex, insula, and superior temporal gyrus (Schabus et al., 2007). Delta waves have been associated with increases of brain activity in the inferior frontal gyrus, brainstem, cerebellum, prefrontal, posterior cingulate cortex, and parahippocampal gyrus (Dang-Vu et al., 2008). Beside identifying the brain structures involved in the generation, propagation, or modulation of NREM sleep oscillations, these studies emphasize that NREM sleep is not a state of brain quiescence characterized by persistent decrease in brain activity, but a state during which brain activity is temporally organized in specific oscillations.

**REM sleep**

In contrast to NREM sleep, REM sleep is characterized by a sustained neuronal activity (Steriade and McCarley, 1990; Jones, 1994) and, correspondingly, by high cerebral requirements (Maquet et al., 1990) and blood flow (Madsen et al., 1991a; Lerou et al., 1999) (Figure 6.2). In this active but sleeping brain, some areas are particularly active, even more than during wakefulness, while others have lower than average regional activity.

During REM sleep, significant rCBF increases have been found in the pontine tegmentum, thalamic nuclei, limbic and paralimbic areas (amygdaloid complex, hippocampal formation (Braun et al., 1997; Nofzinger et al., 1997) and anterior cingulate cortex (Maquet et al., 1996; Braun et al., 1997; Nofzinger et al., 1997). Posterior cortices in temporopolar-occipital areas were also found to be activated (Braun et al., 1997; Wohrle et al., 2003), although less consistently. In contrast, the inferior and middle dorsal lateral prefrontal gyri and the inferior parietal cortex were the least active brain regions (Maquet et al., 1996, 2005; Braun et al., 1997).

Regional brain activity in mesopontine, occipital, and thalamic regions during human REM sleep (Maquet et al., 1996; Braun et al., 1997; Nofzinger et al., 1997, Wohrle et al., 2005) is in keeping with our current understanding of sleep generation in animals. REM sleep is generated by neuronal populations of the mesopontine reticular formation that activate the thalamic nuclei which in turn activate the cortex (Steriade and McCarley, 1990).

The activation of limbic and paralimbic structures, including amygdaloid complexes, hippocampal formation, and anterior cingulate cortex, is constantly reported (Maquet et al., 1996; Braun et al., 1997; Nofzinger et al., 1997). Animal data show that the amygdala plays a role in REM sleep modulation. For example, pentagastrin-occupied (PGO) waves, a major component of REM sleep phasic endogenous activity, were increased in cats by electrical stimulation of the central nucleus of amygdala (CNA) (Czeh et al., 1998), while the cocaine (a monoamine agonist) injections in the same nucleus enhanced both REM sleep and PGO activity (Calvo et al., 1996).
Fig. 6.2. Cerebral glucose metabolism (CMRGlus) and regional cerebral blood flow (CBF) during rapid eye movement (REM) sleep (first column), deep non-REM (NREM) sleep or slow-wave sleep (SWS) (second column) and wakefulness (third column).

Row A: CMRGlus quantified in the same individual at 1-week interval, using $^{18}$F-fluorodeoxyglucose and positron emission tomography (PET). The three images are displayed at the same brain level using the same color scale. The average CMRGlus during deep NREM sleep (versus wakefulness) is significantly decreased. During REM sleep the CMRGlus is as high as during wakefulness.

Row B1: Distribution of the highest regional brain activity, as assessed by CBF measurement using PET, during wakefulness and REM sleep. The most active regions during wakefulness are located in the polymodal associative cortices in the prefrontal and parietal lobes (both in the medial wall and convexity). During REM sleep, the most active areas are located in the pontine tegmentum, the thalami, the amygdaloid complexes, and the anterior cingulate cortex. Other data (not shown) have shown a large activity in the occipital cortices, the insula, and the hippocampus (Braun et al., 1997).

Row B2: Distribution of the lowest regional brain activity, as assessed by CBF measurement using PET, during NREM and REM sleep. In both sleep stages, the least active regions are located in the polymodal associative cortices in the prefrontal and parietal lobes (convexity). During NREM sleep, the thalamus and thalami are also particularly deactivated.

Likewise, the rebound of REM sleep induced by micro-injections of gamma aminobutyric acid (GABA) agonist into the peripeduncular gray matter elicited a significant increase in c-fos labeling in the amygdala (Sastre et al., 2000).

The activated temporo-occipital areas during REM sleep (Braun et al., 1997) include inferior temporal cortex and fusiform gyrus, which are extrastriate cortices belonging to the ventral visual stream. Functional connectivity of these areas is also modified during REM sleep. The functional relationship between striate and extrastriate cortices, usually excitatory during wakefulness, is reversed during REM sleep (Braun et al., 1997, 1998). Likewise, the functional relationship between the amygdala and the temporal and occipital cortices is different during REM sleep than during wakefulness or NREM sleep (Maquet and Phillips, 1998). This pattern suggests that not only the functional neuroanatomy but also the functional interactions between neuronal populations are different during REM sleep than during wakefulness.

Pontine waves or PGO waves are also primary features of REM sleep. In rats, the generator of the pontine waves projects to a set of brain areas shown to be active in human REM sleep: the occipital cortex, the entorhinal cortex, the hippocampus, and the amygdala, as well as brainstem structures participating in the generation of REM sleep (Datta et al., 1998). In cats, although most easily recorded in the pons (Jouvet, 1967), the lateral geniculate bodies (Milner et al., 1961), and the occipital cortex (Mourè et al., 1963), PGO waves are observed in many parts of the brain,
Idiopathic insomnia is a lifelong inability to obtain adequate sleep that is persistently associated with decreased sleep efficiency, increased sleep latency, and decreased sleep duration. The condition is characterized by subjective complaints of sleeplessness, daytime sleepiness, and fatigue. The functional neuroimaging of idiopathic insomnia is complex and involves multiple brain regions. In a recent study, using functional magnetic resonance imaging (fMRI), researchers found that the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC) were more active in patients with idiopathic insomnia compared to healthy controls. This increased activity in these regions may reflect a compensatory mechanism to improve sleep efficiency. Additionally, decreased activity in the basal ganglia and thalamus was observed, which may indicate a disruption in the balance of excitatory and inhibitory inputs to these structures.

In conclusion, idiopathic insomnia is a complex disorder that involves multiple brain regions. Further research is needed to better understand the underlying mechanisms and develop effective treatments.
disorder (referred to as primary insomnia in these reports). Using technetium-99m-hexamethylene-propyleneamine Oxime ($^{99m}$Tc-HM-PAO), a gamma-emitting radionuclide imaging agent, regional CBF was estimated in 5 insomniacs and 4 normal sleepers during NREM sleep. Patients with insomnia revealed major CBF decreases in the basal ganglia, frontal medial, occipital, and parietal cortices. These results suggest that idiopathic insomnia is associated with an abnormal pattern of regional brain function during NREM sleep that particularly involves basal ganglia (Smith et al., 2002).

More recently, regional cerebral glucose metabolism (CMRglu) was measured using $^{18}$F-fluorodeoxyglucose ($^{18}$FDG) PET in 7 patients with idiopathic insomnia and 20 healthy age- and gender-matched subjects during waking and NREM sleep (Nozinger et al., 2004b). Insomniacs patients showed increased global CMRglu during sleep as compared to healthy subjects, suggesting an overall cortical hyperarousal in insomnia. In addition, insomniacs patients had a smaller decline, related to healthy subjects, in CMRglu from waking to sleep states in the ascending reticular activating system, hypothalamus, thalamus, insular cortex, amygdala, hippocampus, anterior cingulate, and medial prefrontal cortices. During wakefulness, reduced metabolism, as compared to healthy subjects, was detected in the prefrontal cortex bilaterally, in the left superior temporal, parietal, and occipital cortices and in the thalamus, hypothalamus, and brainstem reticular formation. Taken together, these findings confirm that regional brain activity does not normally progress from waking to sleep states in patients with insomnia. Moreover, it was proposed that daytime fatigue resulting from inefficient sleep may be reflected by decreased activity in the prefrontal cortex (Nozinger et al., 2004a) (Figure 6.3).

Interestingly, 4 of the insomnia patients from the Smith's study were rescanned after cognitive behavioral therapy (Smith et al., 2005). Sleep latency was reduced by at least 45% and there was a global 24% increase in CBF, with significant increases in the basal ganglia after this psychotherapeutic treatment. Such an increase in brain activity has been proposed to reflect the normalization of sleep homeostatic processes. These promising results will certainly inspire further investigations on the effects of psychotherapy on brain functioning in insomnia.

Depression
The most common primary diagnosis in patients presenting with a complaint of insomnia is depression (Hensan, 2000). Depression is a subclass of mood disorders, which are psychiatric disorders characterized by either one or more episodes of depression, or partial or full mania or hypomanic episodes. Depressive disorders include major depressive disorder, diagnosed in people who have experienced at least one major depressive episode. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994) provides diagnostic criteria for major depression. At least five symptoms must be present for the same 2-week period, nearly every day, and at least one symptom must be either depressed

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**Fig. 6.3.** Regional cerebral glucose metabolism (CMRglu) in patients with insomnia assessed during both waking and nonrapid eye movement sleep states by using $^{18}$F-fluorodeoxyglucose positron emission tomography.

Panel A: Brain structures that did not show decreased glucose metabolic rate from wakefulness to sleep states in patients with insomnia.

Panel B: Brain structures where relative glucose metabolism during wakefulness was higher in healthy subjects than in patients with insomnia. (Reproduced from Nozinger et al. (2004a), with permission from the American Journal of Psychiatry, Copyright 2004, American Psychiatric Association.)
mood or loss of interest or pleasure. Other symptoms of major depressive episodes include insomnia or hypersomnia, significant weight loss or weight gain, psychomotor activity or retardation, fatigue, feelings of worthlessness or excessive or inappropriate guilt, poor concentration, recurrent thoughts of death, and recurrent suicidal ideation. The disease is classified as dysthmic when the full criteria for major depression are not met and when individuals are chronically depressed for at least 2 years. The association between typical features of depression, insomnia, and, more rarely, excessive sleepiness (AASM, 2001) remains not clearly understood.

In depressed patients, modifications of sleep architecture are characterized by reduced SWS, onset of the first episode of REM sleep, and increased phasic REM sleep (Thase, 1998).

In the following sections, we will present studies conducted in depressed patients during wakefulness, after sleep deprivation, during NREM, and during REM sleep.

**Wakefulness Neuroimaging in Depression**

Neuroimaging studies in depressed patients during wakefulness indicate that dysfunction of the prefrontal cortical and striatal systems, which normally modulate limbic and brainstem structures, play an important role in the pathogenesis of depressive symptoms (Mayberg, 1997; Drevets, 2001). Abnormalities within orbital and medial prefrontal cortex areas persist following symptom remission (Drevets, 2000). These findings involve interconnected neural circuits in which dysfunction of neurotransmission may result in the depressive symptoms (Drevets, 2000, 2001).

The Hamilton Depression Rating Scale (HDRS) is widely used to measure the severity of depression in mood disorders. Voxelwise correlation maps have shown that total HDRS score correlates with metabolism as measured by 18F-FDG PET during wakefulness in a large set of cerebral areas, including limbic structures, thalamus, and basal ganglia. Moreover, sleep disturbance, a distinct symptom cluster included in the HDRS, correlated positively with glucose metabolism in limbic structures and basal ganglia (Milak et al., 2005).

**Sleep Deprivation in Depression**

Interestingly, sleep deprivation has rapid beneficial effects in about 60% of depressed patients (Wirz-Justice and Van den Hoofdakker, 1999). Responders to sleep deprivation are usually patients with high behavioral activation and low levels of tiredness (Szuba et al., 1991; Bouthuys et al., 1995). These findings suggest an increased arousal in depressed patients (Clark and Watson, 1991; Joiner et al., 1999), a hypothesis that finds support in functional neuroimaging data. Beta activity is proposed as an EEG marker of arousal during sleep. In an 18FDG PET study (Nozinger et al., 2000) beta power was negatively correlated with subjective sleep quality, in both normal and depressed subjects, although depressed patients exhibited increased beta activity during the night compared to normal controls. Interestingly, beta power was correlated with glucose metabolism levels in the ventromedial prefrontal cortex, a region amongst the most deactivated during consolidated SWS (see above) (Nozinger et al., 2000).

These clinical, electrophysiological, and neuroimaging studies provide some evidence in keeping with the hypothesis of increased hyperarousal in depressed patients. Nevertheless, pathophysiological mechanisms linking hyperarousal with depression as well as insomnia with depression remain to be established.

The physiological mechanisms underpinning the beneficial effects of sleep deprivation are complex and not completely understood yet. It has been hypothesized that REM sleep pressure is enhanced in depressed patients. In depressed patients responding favorably to sleep deprivation, as compared to nonresponders, baseline brain activity during wakefulness was reported to be higher in the anterior cingulate cortex (Wu et al., 1992; Clark et al., 2001) and/or the nearby medial frontal cortex (Ebert et al., 1991, 1994b; Wu et al., 1999; Clark et al., 2001), then to decrease significantly after sleep deprivation as compared to wakefulness. A similar pattern of brain activity was observed in elderly depressed patients, including normalization after total sleep deprivation associated with antidepressant treatment (Smith et al., 1999). In addition, the normalization of anterior cingulate metabolism persisted even after recovery sleep (Smith et al., 1999). Interestingly, it was also shown that sleep deprivation responders, as compared to nonresponders, exhibit a significant decrease in relative basal ganglia D2 receptor occupancy after sleep deprivation (Ebert et al., 1994a). These results suggest that the antidepressant benefits of sleep deprivation are correlated with enhanced endogenous dopamine release in responders, as compared to nonresponders. These results corroborate previous hypotheses of dopaminergic participation in the therapeutic action of sleep deprivation, and indirectly support a dopamine hypothesis of depression (Ebert et al., 1994a).

Recently, a preliminary work studied the effect of concomitant sleep deprivation and antidepressant medication in 6 depressed patients (Wu et al., 2008). They were administered the serotonergic antidepressant sertraline for a week and then underwent FDG
PET before and after total sleep deprivation. Glucose metabolism decreased in the inferior frontal gyrus and inferior fronto-orbital frontal cortex and increased in the dorsolateral prefrontal cortex, in correlation with reduced score of HDRS.

**NREM SLEEP NEUROIMAGING IN DEPRESSION**

It was shown that whole-brain absolute CMRglu during NREM sleep is higher in depressed patients than in normal subjects (Ho et al., 1996). The greatest increases were observed in the posterior cingulate, the amygdala, the hippocampus, and the occipital and temporal cortex. Significant reductions of relative CMRglu were found in the prefrontal and anterior cingulate cortices, caudate nucleus, and medial thalamus.

More recently, depressed patients showed smaller decreases than controls in relative regional CMRglu from presleep wakefulness to NREM sleep in the left and right lateral frontal gyri, right medial prefrontal cortex, right superior and middle temporal gyri, insula, right posterior cingulate cortex, lingual gyrus, striate cortex, cerebellar vermis, and left thalamus (Germain et al., 2004b). These results suggest that transition from wakefulness to NREM sleep in depressed patients is characterized by persistent "elevated" activity in frontoparietal regions and thalamus. Intuitively, it is as if the low frontal metabolism during wakefulness could not be further decreased during NREM sleep, as is the case for normal subjects. These findings suggest that abnormal thalamocortical network function may underpin sleep abnormalities and nonrestorative sleep complaints in depressed patients (Germain et al., 2004b).

**REM SLEEP NEUROIMAGING IN DEPRESSION**

Anterior paralimbic areas (anterior cingulate cortex, right insula, right parahippocampal gyrus) were shown to be less active in depressed patients than in normal subjects, during REM sleep, as compared to wakefulness (Nofzinger et al., 1999). The spatial extent of paralimbic activation from wake to REM sleep was shown to be greater in the depressed patients as compared to healthy controls (Nofzinger et al., 2004b). Moreover, from waking to REM sleep, depressed patients showed greater activation in bilateral dorsolateral prefrontal, left premotor, primary sensory motor, and left parietal cortices, as well as in the midbrain reticular formation (Nofzinger et al., 2004b) and in the tectal area, inferior temporal cortex, amygdala, and subicular complex (Nofzinger et al., 1999).

The density of REM (number of REMs per minute of REM sleep) has been correlated with the severity of the depression (Thase et al., 1997; Buysse et al., 1999).

Average REM count (an automated analog of REM density) was positively correlated with regional CMRglu bilaterally in the striate cortex, the posterior parietal cortices, and in the medial and ventrolateral prefrontal cortices in depressed patients compared to healthy controls. Moreover, it was negatively correlated with regional CMRglu in areas corresponding bilaterally to the lateral occipital cortex, cuneus, temporal cortices, and parahippocampal gyrus (Germain et al., 2004a). For the authors, these results suggest that average REM count may be a marker of hyperfrontality during REM sleep in depressed patients.

Depression (an antidepressant drug) increases CMRglu in anterior cingulate, medial prefrontal cortex, and right anterior insula from waking to REM sleep. After analysis, this effect was linked to a reduction in waking relative metabolism in these structures following treatment in the absence of a significant effect on REM sleep relative metabolism (Nofzinger et al., 2001).

**Summary**

Taken together, these data suggest a close link between mood alteration and activity in limbic and paralimbic structures. Especially, it suggests that hyperactivity in the anterior cingulate cortex of depressed patients during wakefulness may hinder further increases in REM sleep. From this perspective, sleep deprivation would alleviate depression symptoms in decreasing abnormally elevated activity in the anterior cingulate cortex during wakefulness. However, available data remain limited and further studies using more detailed designs are needed to understand the causes and consequences of these mesial frontal metabolic disturbances.

Overall, relationships between sleep, insomnia, and depression open a neurobiological window to the understanding of the pathophysiological mechanisms of depression which should be extensively explored in the future.

**Narcolepsy**

Narcolepsy is a disorder which is characterized by excessive sleepiness that is typically associated with cataplexy, sleep paralysis, and hypnagogic hallucinations (AASM, 2001).

To the best of our knowledge, in narcoleptic patients, the widespread functional neurometabolism of waking state, REM sleep, or SWS is not yet fully described. Nor are the neural correlates characterized of other characteristic symptoms such as cataplexy, hypnagogic/ hypnagogic hallucinations, or sleep paralysis.

Early observations using 133Xe inhalation showed that, during wakefulness, brainstem and cerebellar
PEIT before and after total sleep deprivation. Glucose metabolism decreased in the inferior frontal gyrus and primary motor/bilateral ventral frontal cortices and increased in the dorsolateral prefrontal cortex, in correlation with reduced score of HIRRS.

NREM SLEEP NEOIMAGING IN DEPRESSION

It was shown that whole-brain absolute CMRglu during NREM sleep is higher in depressed patients than in normal subjects (Ho et al., 1996). The greatest increases were observed in the posterior cingulate, the amygdala, the hypothalamus, and the parahippocampal gyrus. Significant reductions of relative CMRglu were found in the prefrontal and anterior cingulate cortices, caudate nucleus, and medial thalamus.

More recently, depressed patients showed smaller decreases than controls in relative regional CMRglu from presleep wakefulness to NREM sleep in the left and right laterodorsal frontal gyr, right medial prefrontal cortex, right superior and middle temporal gyr, insula, right posterior cingulate cortex, lingual gyrus, striate cortex, cerebellum vermis, and left thalamus (Germaine et al., 2004b). These results suggest that transition from wakefulness to NREM sleep in depressed patients is characterized by persistent "elevated" activity in frontoparietal regions and thalamus. Intuitively, it is as if the low frontal metabolism during wakefulness could not be further decreased during NREM sleep, as is the case for normal subjects. These findings suggest that abnormal thalamocortical network function may underpin sleep abnormalities and contribute to excessive sleep complaints in depressed patients (Germaine et al., 2004b).

REM SLEEP NEOIMAGING IN DEPRESSION

Anterior paralimbic areas (anterior cingulate cortex, right insula, right parahippocampal gyrus) were shown to be less active in depressed patients than in normal subjects, during REM sleep, as compared to wakefulness (Nozinger et al., 1999). The spatial extent of paralimbic activation from wakefulness to REM sleep was shown to be greater in the depressed patients as compared to healthy controls (Nozinger et al., 2004b). Moreover, from waking to REM sleep, depressed patients showed greater activation in bilateral dorsolateral prefrontal, left premotor, primary sensorimotor, and left parietal cortices, as well as in the midbrain reticular formation (Nozinger et al., 2004b) and in the frontal, inferior temporal cortex, amygdala, and subicular complex (Nozinger et al., 1999).

The density of REM (number of REMs per minute of REM sleep) has been correlated with the severity of the depression (Thase et al., 1997; Hyslop et al., 1999). Average REM count (an automated analog of REM density) was positively correlated bilaterally in the striate cortex, the posterior paralimbic cortices, and in the medial and ventrolateral prefrontal cortices in depressed patients compared to healthy controls. Moreover, it was negatively correlated with regional CMRglu in areas corresponding bilaterally to the lateral occipital cortex, cuneus, temporal cortices, and parahippocampal gyr (Germaine et al., 2004a). For the authors, these results suggest that average REM count may be a marker of hypofrontality during REM sleep in depressed patients.

Hypopnoea (an antidepressant drug) increases CMRglu in anterior cingulate, medial prefrontal cortex, and right anterior insula from waking to REM sleep. After analysis, this effect was linked to a reduction in waking relative metabolism in these structures following treatment in the absence of a significant effect on REM sleep relative metabolism (Nozinger et al., 2001).

SUMMARY

Taken together, these data suggest a close link between mood alteration and activity in limbic and paralimbic structures. Especially, it suggests that hyperactivity in the anterior cingulate cortex of depressed patients during wakefulness may hinder further increases in NREM sleep. From this perspective, sleep deprivation would alleviate depression symptoms in decreasing abnormally elevated activity in the anterior cingulate cortex during wakefulness. However, available data remain limited and further studies using more detailed designs are needed to understand the causes and consequences of these frontal metabolic disturbances.

Overall, relationships between sleep, insomnia, and depression open a neurobiological window to the understanding of the pathophysiological mechanisms of depression which should be extensively exploited in the future.

Narcolepsy

Narcolepsy is a disorder which is characterized by excessive sleepiness that is typically associated with cataplexy, sleep paralysis, and hypnagogic hallucinations (AASM, 2001).

To the best of our knowledge, in narcoleptic patients, the voxswise functional neuroanatomy of waking state, REM sleep, or SWS is not yet fully described. Nor are the neural correlates characterized of other characteristic symptoms such as cataplexy, hypnopompic/hypnagogic hallucinations, or sleep paralysis.

Early observations suggested that, during wakefulness, brainstorm and cerebellar blood flow was lower in narcoleptic patients than in normal subjects (Meyer et al., 1980). In contrast, after sleep onset (3 out of 15 in REM sleep), the CBF increased in all areas, and particularly in temporoparietal regions. This pattern was supposedly attributed to dreaming activity, in line with prior reports showing that regional blood flow was increased in temporoparietal areas during visual dreaming and hypnagogic hallucinations (Maquet et al., 1988, 1997).

In another study, 6 narcoleptic patients underwent 99mTc-HMPAO SPECT and showed similar HMPAO uptake in waking state and REM sleep (Abernethy et al., 1995), suggesting a similar overall cortical activity. An activation of parietal regions during REM sleep was shown with data analysis by regions of interest (Aisenbaurm et al., 1995). The latter result is intriguing given the parietal deactivation usually observed by PET studies during normal REM sleep (Maquet, 2000). Overall, further studies are needed to confirm these results on a broader population.

Data describing the neural correlates of cataplexy in narcoleptic patients are very scarce. One SPECT study was conducted on 2 patients during a cataplexy episode compared to REM sleep or baseline waking period (Hong et al., 2006). During cataplexy, perfusion increased in limbic areas (including amygdala) and basal ganglia, thalam, premotor cortices, sensorimotor cortices, and brainstem, whereas perfusion decreased in dreaming activity, in line with the notion that cataplexy and amygdala activity might be correlated to emotional processing that is usually reported as a powerful trigger of cataplexy. However, such hyperperfusion in the parietal lobes and amygdala complexes may relate to concomitant emotional processing that is usually reported as a powerful trigger of cataplexy. Hypoperfusion in the parietal lobes and amygdala complexes was not found in a recent single case report (Chalbas et al., 2007).

A very recent event-related fMRI study was performed on narcoleptic patients and controls while they watched sequences of humorous pictures. This study is based on the clinical observation that cataplexy episodes are often triggered by positive emotions (e.g. hearing or telling jokes). A group comparison revealed that humorous pictures elicited reduced hypothalamic response together with enhanced amygdala response in the narcoleptic patients. These results suggest that hypothalamic hyperactivity in activity physiologically modulates the processing of emotional inputs within the amygdala, and that suprapoietic mechanisms of cataplexy might involve a dysfunction of hypothalamic-amygdala interactions triggered by positive emotions (Schwartz et al., 2008). Another fMRI study confirmed an increase of activity in the emotional network in narcoleptic patients compared to controls while viewing humorous cartoons (Reiss et al., 2008). Increased activity was also observed in the right inferior frontal gyr, an area involved in inhibition (Aron et al., 2004). In addition a recent study was showed in 1 patient experiencing a cataplectic attack. For authors, these findings suggest an overdrive of the emotional circuity and possible compensatory suppression by cortical inhibitory regions in cataplexy (Reiss et al., 2008). Given the role of acetylcholine as an important neurotransmitter of NREM sleep (see above), cholinergic dysfunction was hypothesized to underlie narcolepsy. However, at present, the available PET data did not show any change in muscarinic cholinergic receptors in narcoleptic patients (Sudi et al., 1995).

Similarly, the dopamine system has been probed by PET in narcoleptic patients because increased dopamine D2 binding was shown in the brain of deceased narcoleptic patients (Aldrich et al., 1992; Kish et al., 1992). Results remain controversial. One SPECT study has shown that D2 receptor binding in the striatal dopaminergic system was elevated and correlated with the frequency of catapletic and sleep attacks in 7 patients with narcolepsy (Eisensehle et al., 2003a). However, this finding was not confirmed by other PET (Rime et al., 1995, 1996; Macfarlane et al., 1997) or SPECT (Hublin et al., 1994; Staedt et al., 1996) studies. The dopamine-related dysregulation might be related to the drug treatment of narcoleptic patients. Indeed, considerable increase in the uptake of 123I-iopana, a specific D2 receptor ligand, was observed in the striatum of narcoleptic during treatment in young patients older than 31 years who had undergone prolonged treatment (Kian et al., 1994). Likewise, despite the fact that the binding of ibodencarazide (HEC, a highly selective central nervous system dopamine D2 receptor ligand) was similar in narcoleptic patients and normal controls, treatment by stimulants and/or antidepressants for 3 months significantly changed the ligand uptake in 4 out of 5 patients (Staedt et al., 1996). Collectively, these neuroimaging results suggest that the reported postmortem increase in dopamine binding might be due to the possible effect of prior treatment rather than intrinsic modifications.

Two fMRI studies assessed the effects of stimulant drugs on cerebral function in narcoleptic patients. The first one tested the effect of modafinil, a wakefulness-promoting drug (Ellis et al., 1999). In normal subjects, larger brain responses to a multiplexed visual and auditory stimulation paradigm were found at 10.00 hours than at 15.00 hours in visual areas, but not in auditory areas, suggesting time-of-day influences. Surprisingly, the reverse pattern of activity was observed in a group of 12 narcoleptic patients, with higher activity at 15.00 hours than at 10.00 hours, suggesting a difficulty of modafinil administration did not modify the average level of activation in either normal subjects or narcoleptics.
These elements suggest that hypocretin deficiency may represent a specific clinical context as a marker of hypothalamic dysfunction rather than an immediate cause of sleep-wake disturbance (Baumann and Bassetti, 2005).

Differences in brain morphology that are not identifiable in routine structural MRI can be investigated using the technique of voxel-based morphometry (VBM) that compares the brain structure of patients and controls assessed by high-quality MRI (Ashburner and Friston, 2000, 2001). At present, VBM studies have reported equivocal results in narcoleptic patients. A first study did not show any structural change in brains of patients with hypocretin-deficient narcolepsy (Overeem et al., 2003). These authors suggested that narcolepsy is either associated with microscopic changes untractable by VBM or that functional abnormalities of hypocretin neurons are not associated with structural correlates (Overeem et al., 2003). In another VBM study, however, narcoleptic patients exhibited bilateral cortical gray-matter reductions predominantly in inferior temporal and inferior frontal brain regions (Kaufmann et al., 2002). Relative global gray-matter loss was independent of disease duration or medication history and there were no significant subcortical gray-matter alterations. Still another VBM study detected a significant bilateral decrease in hypothalamic gray-matter concentration in narcoleptic patients related to unaffected healthy controls (Draganzik et al., 2002). Decreased gray-matter concentration was also observed in the vermis, the superior temporal gyrus, and the right nucleus accum- bens. Given the major projection sites of hypocretin-1 (the hypothalamus among others) and hypocretin-2 (the nucleus accumbens among others), the decrease in gray matter was thought to reflect the secondary neuronal loss due to the destruction of specific hypocretin projections (Draganzik et al., 2002). This study was corroborated by another VBM study (Buskova et al., 2006). Another VBM study found significant gray-matter loss in the right prefrontal and fronto-temporal cortex of patients with narcolepsy (Bremner et al., 2005). For the authors, the volume reduction of gray matter in narcoleptic patients could indicate a disease-related atrophy.

Several factors can explain these controversial results, such as possible bias due to inhomogenous patient groups, prestatistical image processing, or history of treatment (Bremner et al., 2005). VBM studies with large sample of drug-naive patients should be performed to advance further in this very complex physiopathology.

Proton magnetic resonance spectroscopy (H-MRS) was used in order to assess the N-acetyl-aspartate (NAA) content in the ventral pontine area (Ellis et al., 1998) and the hypothalamus of narcoleptic
patients (Lodi et al., 2004). In both studies, an analysis of spectral peak area ratios revealed a decrease in the NAA/creatinine-phosphocreatine ratio in narcoleptic patients compared with control subjects. These results were interpreted as a neuronal loss or damage in the ventral pontine area and in the hypothalamus of the narcoleptic patients.

Another 1H-MRS study in 17 narcoleptics patients showed a higher GABA concentration in the medial prefrontal cortex, which was more prominent in patients without nocturnal sleep disturbance (Kim et al., 2008). The authors suggest it might be a compensatory mechanism to reduce nocturnal sleep disturbances in narcolepsy.

The results of the Lodi study (Lodi et al., 2004) were confirmed by an 18F-DG PET study that was used to measure relative difference between CMRGluc of 24 narcoleptic patients and 24 normal controls during wakefulness (Joo et al., 2004) (Figure 6.4). Narcoleptic patients had reduced CMRGluc in bilateral prefrontal, bilateral posterior hypothalamic, and mediodorsal thalamic nuclei (Joo et al., 2004). This study prevails over a SPECT study that was subsequently conducted (Yeon Joo et al., 2005).

**Obstructive sleep apnea syndrome**

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of upper-airway obstruction that occur during sleep, generally associated with a reduction in blood oxygen saturation (AASM, 2001). Population-based epidemiologic studies revealed a high prevalence (1–5% of adult men) of OSAS. These studies also associate OSAS with significant morbidity, such as hypertension, cardiovascular disease, stroke, or motor vehicle accidents (Young et al., 2002).

OSAS has a complex pathophysiology which is not yet completely understood. Several studies suggest that OSAS in all age groups is due to a combination of both anatomic airway narrowing and abnormal upper-airway neuromotor tone. Besides the known anatomic factors, such as craniofacial anomalies, obesity, and adenosinergic hypotension, that contribute to OSAS, clear anatomical contributing factors cannot always be identified (AASM, 2001). This suggests that alterations in upper-airway neuromuscular tone also play an important role in the etiology of OSAS (Arens and Marcus, 2004). The pathophysiology of OSAS also includes enhanced chemoreflex sensitivity and an exaggerated sympathetic response during hypoxic episodes (Capes et al., 2005). Furthermore, it is still a matter of debate whether the cognitive consequences of OSAS are reversible or not (Aloia et al., 2004; Brown, 2005). Functional impairments are often associated with neuropsychological deficits which are often thought to be reversible with appropriate treatment (Aloia et al., 2004; Brown, 2005). In contrast, structural alterations may indicate irreversible cerebral changes and would underpin permanent cognitive impairments (Alchanatis et al., 2004), although this proposal remains a matter of debate in the literature (Gale and Hopkins, 2004). In addition, the specific consequences of sleep fragmentation and hypoxia on cognition and brain function have still to be teased apart and thoroughly characterized.

We will present successively an overview of cognitive alterations, changes in brain structure and function, and finally neuroimaging studies exploring ventilatory control in OSAS.

**Overview of cognitive alterations**

Alterations of mental process, behavior, and interpersonal relations are a common observation in OSAS patients (Brown, 2005). Moreover OSAS has been associated with distinct cognitive alterations in various

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**Fig. 6.4. Cerebral glucose metabolism (CMRGluc) in the hypothalamus and thalamus in narcoleptic patients during wakefulness.**

Bilateral posterior hypothalami and mediodorsolateral thalamic nuclei show hypometabolism in narcoleptic patients compared to controls. (Reproduced with permission from Joo et al. (2004). Copyright 2004. Wiley-Liss, Inc., A Wiley Company.)
domains. Both fragmented sleep and hypoxemia are proposed as the main factors leading to neurocognitive impairment during wakefulness (Berry et al., 1986; Findley et al., 1986, 1995; Bedard et al., 1991; Cheshire et al., 1992; Bonnet, 1993; George et al., 1996; Young et al., 1997). Several studies emphasized the deterioration of executive functions in OSAS patients, including the inability to initiate new mental processes (Naegeli et al., 1995; Feuerstein et al., 1997), deficits in working memory (Greenberg et al., 1987; Naegeli et al., 1995); contextual memory (Harrison et al., 2000), selective attention (Korterba et al., 1998), continuous attention (Korterba et al., 1998), and analysis and synthesis (Greenberg et al., 1987; Naegeli et al., 1995). A meta-analysis showed that untrated patients with OSAS had a negligible impairment of intellectual and verbal functioning but a substantial impairment of vigilance and executive functioning (Beche et al., 2003). In addition, a “cognitive reserve” could be protective against OSAS-related cognitive decline (Alchanatis et al., 2003). Most studies suggest that cognitive impairments improve with nasal continuous positive airway pressure (CPAP) treatment but evidence suggests that some changes may be permanent (Aloia et al., 2004; Brown, 2005). For instance, after CPAP, OSAS patients improved attention/vigilance in most studies and did not improve constructional abilities or psychomotor functioning (Aloia et al., 2004). Intricate neural dysfunction related to these deleterious factors would add to daytime sleepiness to explain the neuropsychological deterioration of OSAS patients (Beche and Gozal, 2002).

Interestingly, several studies have linked OSAS and depression (Struecher and Oden, 2005). Moreover, several authors have demonstrated improvement in depression scores and overall psychopathology by using CPAP therapy (Engelmann et al., 1997).

STRUCTURAL CHANGES

Using VBM in 21 patients with OSAS and in 21 control subjects, structural changes in brain morphology were assessed (Mathey et al., 2002). Diminished regional and often unilateral gray-matter loss was apparent in patients with OSAS in multiple brain sites involved in motor regulation of the upper airway as well as in various cognitive functions, including the frontal and parietal cortex, temporal lobe, anterior cingulate, hippocampus, and cerebellum. Another VBM study conducted in 7 OSAS patients and 7 controls showed a significantly lower gray-matter concentration solely within the left hippocampus in the OSAS patients (Morrell et al., 2003). There was no difference in total gray-matter volume between the two groups. In a more recent VBM study (27 OSAS patients and 24 controls), it has been found that there are no gray-matter volume deficits or focal structural changes in severe OSAS patients. Whole-brain volume decreases without focal changes after 6 months of CPAP treatment (O'Donohue et al., 2003).

Another study compared both neuropsychological and neuropsychophysical effects of hypoxia in patients with other carbon monoxide poisoning or OSAS (Gale and Hopkins, 2004). Brain imaging showed a hippocampal atrophy in both groups even though a linear relationship between hippocampal volume and memory performance was found for only a subset of selected tests (the delayed recall or the Rey-Osterreicht Complex Figure Design and Trial 6 of the Rey Auditory Verbal Learning Test, among others), and only in the OSAS group. Hippocampal volume was related to performance on nonverbal information processing (Wechsler Adult Intelligence Scale – Revised Block Design). Further data will be necessary to delineate better the specificity and contribution of hippocampal atrophy in OSAS.

CHANGES IN BRAIN FUNCTION

As described earlier, cognitive executive functions, associated with specific prefrontal-subcortical brain circuits, are dysfunctional in OSAS patients (Alchanatis et al., 2004). Another study, using single-voxel 1H-MRS, attempted to demonstrate that OSAS can induce frontal cortical, parieto-occipital and frontal parietal-occipital gray matter. Magnetic resonance spectra were obtained from prefrontal cortex, parieto-occipital and frontal parietal-occipital white matter. NAA-to-creatine and choline-to-creatine ratios were significantly lower in the frontal white matter of OSAS patients when compared to controls. Absolute concentrations of NAA and choline were also significantly reduced in the frontal white matter of OSAS patients (Alchanatis et al., 2004). These findings may offer an explanation for the sometimes irreversible cognitive deficits associated with OSAS. Despite these results, which suggest an implication of frontal-lobe white-matter lesion in daytime cognitive dysfunction, it still lacks a direct relationship between frontal dysfunction and cognitive impairments. Likewise, some clarification is needed to show the respective roles (in cognitive alterations supposed to be frontal) of hypoxia, sleep fragmentation, or sleep deprivation which occur during OSAS.

Another 1H-MRS study in OSAS patients showed that, in the left hippocampal area, the N-acetyl-containing/creatinine-containing compounds ratio was significantly increased (Hartle et al., 2004). Analysis indicated that this was probably due to a decrease in creatine-containing
FUNCTIONAL NEUROIMAGING IN SLEEP, SLEEP DEPRIVATION, AND SLEEP DISORDERS

compounds which was correlated with worse OSAS severity and neurocognitive performance. Authors suggest that the metabolic changes in the hippocampal area represent adjustments to brain bioenergetics and may reflect the different susceptibility of this tissue to hypoxic damage in OSAS, as in ischemic preconditioning. An earlier and less reflective \(^1\)H-MRS study in 23 OSAS patients showed that the NAA-to-choline ratio in cerebral white matter was significantly lower in patients with moderate to severe OSAS than in patients with mild OSAS and healthy subjects (Kamba et al., 1997). This finding suggests the presence of cerebral damage, probably caused by repeated apneic episodes. In addition, a study by Halbower et al. (2006) showed a decrease in the NAA-to-choline ratio in the left hippocampus and in the right frontal cortex using the same technique in a pediatric population with OSAS. Together VBM and spectroscopy studies point to an atrophy and/or dysfunction of hippocampal regions in OSAS.

Long-term consequences of OSAS have been more rarely assessed after nCPAP treatment. An early \(^99\)mTc-HMPAO SPECT study in 14 adult OSAS patients (Ficker et al., 1997) reported a marked frontal hyperperfusion in 5 patients. In distinction, regional analysis showed a reduced perfusion in the left parietal region. It is noteworthy that all these changes were completely reversed by effective nCPAP therapy, suggesting that the main deleterious effects of OSAS on brain activity are reversible. The authors suggest that there might be an apnea-associated effect of local vascular autoregulation mechanisms acting to compensate systemic blood flow alterations or blood gas changes in OSAS. Using \(^1\)H-MRS, a study showed that NAA in the parietal-occipital cortex was significantly reduced more in 14 OSAS patients than in controls, but this reduction persisted after nCPAP therapy despite clinical, neuropsychological, and neurophysiological normalization (Tonon et al., 2007). In addition, mandibular advancement led to decreased fMRI response in the left cingulate gyrus and the bilateral prefrontal cortices in 12 healthy subjects during induced respiratory stress (Hashimoto et al., 2006). Simultaneously, the subjective effects of this treatment were assessed by a visual analog scale and confirmed successful reduction of respiratory stress.

Changes in ventilatory control

In OSAS patients, apnea has considerable hemodynamic consequences that are mediated by a complex cascade of physiological events. Repetitive episodes of apnea trigger marked fluctuations in both blood pressure and heart rate, with consequent effects on the estimates of cardiovascular variability (Kryger et al., 2000). Several important regulatory mechanisms in cardiovascular homeostasis seem to be impaired in OSAS patients. Specific chemoceptors seem to be implicated in the pathophysiology of OSAS (Mateika and Ellyth, 2003). For instance, the ventilatory response to carbon dioxide is elevated in OSAS patients (Mateika and Ellyth, 2003). The partial pressure of carbon dioxide that delimits the carbon dioxide ventilatory recruitment threshold is elevated in patients with OSAS (Mateika and Ellyth, 2003). An altered autonomic balance has been suggested as one possible pathogenic factor. This autonomic dysfunction has been thought to be implicated in the subsequent development of cardiovascular diseases in patients with OSAS. Several fMRI studies have been conducted in OSAS patients to characterize the neural correlates of integrated afferent airway signals with autonomic outflow and airway motor response (Harper et al., 2003; Henderson et al., 2003; Macey et al., 2003, 2006). For instance, altered neuronal response after Valsalva maneuver was shown in cerebellar, limbic, and motor areas involved in the control of diaphragmatic and upper-airway muscles (Figure 6.5). Enhanced sympathetic outflow after a forehead cold pressor challenge results in both diminished and exaggerated responses in limbic area, cerebellar, frontal cortex, and thalamus.

An fMRI study evaluated the brain activity changes during baseline and expiratory loading conditions in 9 OSAS patients and 16 controls (Macey et al., 2003). Reduced neural signals emerged in OSAS patients within the frontal cortex, anterior cingulate, cerebellar dentate nucleus, dorsal pons, anterior insula, and lenticuliform nuclei. Signal increases in OSAS over control subjects developed in the dorsal midbrain, hippocampus, quadrangular cerebellar lobule, ventral midbrain, and ventral pons. Fastigial nuclei and the amygdala showed substantially increased variability in OSAS subjects. No group differences were found in the thalamus. Both groups developed similar expiratory loading pressures, but appropriate autonomic responses did not emerge in OSAS patients. A more recent fMRI study evaluated the brain activity changes during baseline and inspiratory loading in 7 OSAS patients and 11 controls (Macey et al., 2006). A number of cortical and subcortical areas mediating sensory and autonomic processes, and motor timing were affected. Altered signals appeared in primary sensory thalamus and sensory cortex, supplementary motor cortex, cerebellar cortex and deep nuclei, cingulate, medial temporal, and insular cortices, right hippocampus, and midbrain (Macey et al., 2006).

These altered brain activation patterns, during waking, could reflect neural dysfunctions that mediate...
the prominently diminished upper-airway tone which occurs in OSAS patients during sleep.

**Summary**

Altogether, these findings suggest that neuropsychological damage in OSAS is brought about by various alterations in prefrontal cortex, hippocampal and parietal cortex. Even if abnormal brain activations are reversible under nCPAP, several studies have suggested that not all neuropsychological damage disappears after nCPAP (Bedard et al., 1993; Feuerstein et al., 1997; Naegle et al., 1998). According, structural brain changes have been reported in OSAS patients. Although the basic pathophysiological mechanisms are not completely understood, a deregulation in the autonomic regulation seems to have an important role in these mechanisms. However, it is important to notice that peripheral factors may confound the deficits observed in studies focused on OSAS patients, including exaggerated body mass index and motivational problems (Tasali and Van Cauter, 2002; Spiegel et al., 2004).

**Abnormal motor behaviors during sleep**

Abnormal motor behaviors during sleep include the periodic limb movements and RBD, a specific parasomnia syndrome associated with REM sleep. Abnormal motor behaviors are a common cause of sleep disturbance and the understanding of the underlying physiopathology should be useful in the management (diagnostic and prognostic information) of insomnia (Montplaisir et al., 1994).

**Periodic limb movements**

Periodic limb movement disorder during sleep (PLMS) and RLS are distinct but overlapping syndromes. PLMS is characterized by periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep (ASDA, 1990). RLS is a disorder...
characterized by uncomfortable leg sensations, usually prior to sleep onset, that cause an almost irresistible urge to move the legs (ASDA, 1990).

The diagnosis of PLMS requires the presence of PLMS on polysomnography as well as an associated sleep complaint. RLS, however, is essentially made on clinical grounds. Moreover, PLMS are themselves non-specific, occurring both with RLS and with other sleep disorders (e.g., narcolepsy, sleep apnea syndrome, RBD) as well as in normal individuals (Tan and Ondo, 2000). Thus, the diagnosis of PLMS requires the exclusion of other potential causes for the associated sleep complaint (Lesage and Hening, 2004).

Structural cerebral abnormalities have been reported in patients with idiopathic RLS (Etgen et al., 2005). High-resolution T1-weighted MRI of 51 patients and 51 controls analyzed using VBM revealed a bilateral gray-matter increase in the pulvinar in patients with idiopathic RLS. These authors suggest that changes in thalamic structures are either involved in the pathogenesis of RLS or may reflect a consequence of chronic increase in afferent input of behaviorally relevant information. Finally, an fMRI study also attempted to localize some cerebral generators of leg discomfort and periodic limb movements in RLS (Bucher et al., 1997). The leg discomfort study showed a bilateral activation of the cerebellum and contralateral activation of the thalamus in patients. During a second condition, combining periodic limb movements and sensory leg discomfort, patients also showed activity in the cerebellum and thalamus with additional activation in the red nuclei and brainstem close to the reticular formation. Interestingly, when subjects were asked to imagine PLMS voluntarily, there was no activation in the brainstem, but rather additional activation in the globus pallidus and motor cortex. These results suggest an involuntary mechanism of induction and a subcortical origin for RLS. In addition, a recent VBM study examining 14 patients with idiopathic RLS detected a slightly increased gray-matter density in the ventral hippocampus and in the middle orbitofrontal gyrus (Hornyak et al., 2007).

Recently, 45 idiopathic RLS patients and 30 healthy controls were studied using quantitative whole-brain-based diffusion tensor imaging (Unrath et al., 2008). In the RLS group, regional fractional anisotropy used as a quantitative marker of white-matter integrity was reduced in several subcortical areas, including areas in the proximity of motor and somatosensory cortices, the right hemispheric thalamus (posterior ventral lateral nucleus), in motor projectional fibers, and adjacent to the left anterior cingulum. In addition, high-resolution three-dimensional MRI was performed in 63 idiopathic RLS patients using optimized VBM (Unrath et al., 2007). As compared to controls, regional decreases of gray-matter volume were shown in primary somatosensory cortex and primary motor areas. Clusters in both areas correlated with the severity of RLS symptoms and with disease duration. Together these results show a neocortical and subcortical network of area involving sensorimotor impairment. Incongruent results might be due to differences in populations examined, such as treatment-induced effects on cerebral morphology in RLS, duration of the illness, or methodological issues (size of the samples).

A suprasegmental release of inhibition of descending inhibitory pathways implicating dopaminergic, adrenergic, and opiate systems is thought to be involved in PLMS pathogenesis (Wetter and Pollmacher, 1997). This is supported by the observation of PLMS during spinal anesthesia (Watanabe et al., 1987), for instance. Patients' condition worsens when dopamine antagonists are given (Akpinar, 1982), whereas dopaminergic drugs have been shown to relieve PLMS (Brodeur et al., 1998; Montplaisir et al., 1991, 2000). Staedt et al. have tested the hypothesis of decreased dopaminergic activity in PLMS patients. In a series of SPECT studies, they report a decreased IBZM striatal uptake, indicating a lower D2 receptor occupancy in PLMS patients (Staedt et al., 1993, 1995a, b; Happe et al., 2003). Treating patients with dopamine replacement therapy increased the IBZM binding and improved the sleep quality in these patients (Staedt et al., 1995a).

One study evaluated the striatal pre- and postsynaptic dopamine status in 10 drug-naive patients suffering from both RLS and PLMS and 10 age-matched controls, by means of $^{123}I$ methyl 3 - beta-4-iodophenyl) tropine-2 beta-carboxylate ($^{123}I$-beta-CIT), a ligand of dopamine transporter, and $^{123}I$-IBZM SPECT respectively (Michaud et al., 2002). There was no difference in DA transporter ($^{123}I$-beta-CIT) binding between RLS-PLMS patients and controls. The study of the striatal D2 receptor binding ($^{123}I$-IBZM) revealed again a significantly lower binding in patients as compared with controls. Numerous mechanisms may be responsible for this decrease in D2 receptor binding. Since $^{123}I$-beta-CIT binding is normal, a decreased number of D2 receptors or a decreased affinity of D2 receptors for $^{123}I$-IBZM is more likely than a downregulation of D2 receptors due to an increased level of synaptic dopamine (Michaud et al., 2002).

Fourteen patients with idiopathic RLS and PLMS successfully treated by dopaminergic (e.g., ropinirole) and nondopaminergic (e.g., gabapentin) treatment were investigated while off medication by using $^{123}I$-IBZM and SPECT (Tribol et al., 2004). They were compared to 10 healthy sex- and age-matched control subjects. The patients presented with sleep disturbances, severe
PLMS, and severe RLS symptoms during the period of
sleeping while off medication and did not show any
significant differences in striatal to frontal D1/D2
binding to D2 receptors compared to controls, in con-
trast to the previous study. The authors suggest that
the dopaminergic system in these patients might be
affected elsewhere, possibly in the diencephalonic
part of the dopaminergic system (Tsubi et al., 2004).

These studies support the hypothesis that a central
dopamine dysfunction is involved in the physiopathol-
ogy of RLS-PLMS, although more recent studies spe-
cifically implicate the cerebral metabolism of iron
(A1len, 2004). Iron and the dopaminergic system are
linked since iron is an important cofactor for tyrosine
hydroxylase, the step-limiting enzyme in dopamine
synthesis, and also plays a major role in the function-
ing of postsynaptic D2 receptors (Kryger et al., 2000).

A neuropathologic study (7 RLS brain and 5 normal
brain) has shown a marked decrease in H-ferritin (fer-
ritin heavy chain) and iron staining in RLS substantia
nigra. Transferrin receptor staining on neurelamin-
containing cells was decreased in RLS brains compared
to normal brains, whereas transferrin staining in these
cells was increased (Connor et al., 2003). Using a
special MRI measurement (R*) Allen et al. (2001)
assessed regional brain iron concentrations in 10 sub-
jects (5 with RLS, 5 controls). R* was significantly
decreased in the substantia nigra, and somewhat less
significantly in the putamen, both in proportion to
RLS severity. These results show that this R* MRI
measurement may prove useful in the management
of RLS, and also indicate that brain iron insufficiency
may occur in RLS patients in some brain regions. In
addition, another study found diminished iron concen-
tration across 10 brain regions in early-onset RLS
but not in late-onset RLS when compared to controls
(Farley et al., 2006).

These convergent observations seem to show that
RLS may be a functional disorder resulting from
impaired iron metabolism (i.e., impaired regulation of
transferring receptors) (Connor et al., 2003). Interest-
ingly, altered iron metabolism in lymphocytes was
shown in 24 subjects with RLS as compared with con-
trols. Lymphocytes showed an increase in Ferritport
(a transmembrane protein that transports iron from
the inside to the outside of a cell), implying increased
cellular iron excretion, in the face of increased iron
need (Farley et al., 2008).

REM SLEEP BEHAVIOR DISORDER

RBD is characterized by brisk movements of the body
associated with dream mentation (but usually distur-
b sleep continuity (Schenck et al., 1996). During the noc-
turnal spells, patients behave as if they are acting out
their dream (ASDA, 1997). This disease may be idiopathic
(up to 68%) or associated with other neurologic disorders.
A sizeable proportion of patients with RBD will develop
extrapyramidal disorders (Schenck et al., 1996; Gagnon
et al., 2002, 2004). Lewy body dementia (Frontini et al.,
2003), and multiple system atrophy (PiaZZI et al., 1997;
Gilman et al., 2003). More recently, a strong association
between RBD and alpha-synucleinopathies has been
observed, with the paraosmium often preceding the clinic-
al onset of the neurodegenerative disease (Frontini et al.,
2005; Boeve et al., 2007).

Worthy of note, lesions in the mesopontine tegmen-
tum of cats can lead to the disappearance of muscle
atonia during REM sleep together with dream enact-
ment behavior (Sakai et al., 1979).

A study combining MRS and 251-HMP SPECT in 20
RBD patients and 7 healthy controls during REM sleep
reported significantly decreased blood flow in the upper
portion of both sides of the frontal lobe and in the patients
with RBD, in comparison with normal elderly
subjects (ShiraKawA et al., 2002). Another SPECT study
in 8 RBD patients during wakefulness showed decreased
activity in frontal and temporoparietal cortices but found
increased activity in the pons, putamen, and right hippo-
campus (Mazzu et al., 2006). In addition, brainstem
function was evaluated by 1H-MRS in a 69-year-old man
with idiopathic RBD. An analysis of spectral peak area
ratios revealed an increase in the choline/creatin ratio.
This change suggests that brainstem neurones have func-
tional impairment at the cell membrane level (Miyamoto
et al., 2000). In contrast, one group using 1H-MRS in 15
patients with idiopathic RBD and 15 matched control
subjects failed to reveal any difference in metabolic
peaks of NAA+creatinine, choline+creatinine and myosini-
tol/creatine ratios in the pontine tegumentum and the mid-
brain (Franzo et al., 2002). This result does not support
the hypothesis of marked mesopontine neuronal loss or
1H-MRS detectable metabolic disturbances in idiopathic
RBD. Despite these equivocal results, 1H-MRS may pro-
vide for noninvasive metabolic evaluation of brainstem
neuronal function in RDR and find application in the
differentiation of secondary RBD with neurodegenera-
tive disorders from idiopathic disorders.

Using SPECT and (1H-31)iodobenzylguanidine-(4-chlorophenyl) tegucine labeled
with iodine-123 (IPT), a ligand of striatal presynaptic
dopamine transporters, IPT binding in RBD patients
(\( n = 5 \)) during wakefulness was found to be lower than
in normal controls but higher than in Parkinson patients
(\( n = 10 \)) (Eisenschneider et al., 2000, 2003b). These results
suggest that the number of presynaptic dopamine trans-
porters is decreased in both Parkinson and RBD
patients. Other studies probe the density of striatal
dopaminergic terminals using PET and 11C-dihydroxybenzenate
(11C-DHBZ, a monoamine vesicular transporter

inhibitor used as an in vivo marker for dopamine nerve terminals). Significant reductions in striatal \(^{11}C\)-DTBZ binding characterized 6 elderly subjects with chronic idiopathic RBD, as compared to 19 age-matched controls, particularly in the posterior putamen (Albin et al., 2000). Likewise \(^{11}C\)-DTBZ binding in the striatum was decreased in 13 patients with multiple-system atrophy (MSA) (Gilman et al., 2003). Striatal \(^{11}C\)-DTBZ uptake was inversely correlated with the severity of symptoms in this MSA group. Moreover \(^{125}\)I-iodobenzovesamidol (\(^{125}\)I-IBVM) binding was reduced in the thalamus in this MSA population. \(^{125}\)I-IBVM is a radiotracer that selectively binds to the intraneuronal storage vesicles of cholinergic nerve endings, and is used as a highly specific marker for cerebral cholinergic neurons.

It remains to be shown whether these alterations play a causal role in the pathophysiology of RBD or reflect functional consequences and adaptations to the pathological conditions. Although there is evidence that some Parkinson patients do show excessive nocturnal movements (Trenkwalder, 1998; Happe et al., 2003), it is interesting that only a small percentage of Parkinson patients develop full-blown RBD. This suggests that modifications of other systems of neurotransmission are probably necessary for full-blown RBD to occur.

**CONCLUSIONS**

Brain functional imaging provides unprecedented possibilities to explore brain function during normal and pathological sleep. Nevertheless, brain functional imaging in sleep is still in its infancy, at present mostly restricted to research purposes.

As shown in this review, brain functional imaging in patients affected by sleep disorders may address different kinds of issues. The first topic is the characterization of the cerebral aftermath of sleep disruption due to intrinsic sleep disorders or to extrinsic environmental or medical causes.

The second, more ambitious, aim would be to characterize better the primary physiopathological mechanisms of sleep disorders, or at least their cerebral correlates. This attempt is hampered by several factors. Scanning patients during their sleep is not at all easy, for practical and methodological reasons. It requires some adjustment in the imaging environment and it is never guaranteed that the participant will sleep during data acquisition opportunities. Clinical manifestations in sleep disorders are often unpredictable and transient (e.g., sleepwalking, RBD); thus one cannot predict whether the pathological event will occur during the scanning period. In the same manner, most clinical manifestations induce large movements. These pathological movements during sleep may lead to image artifacts and misinterpretation of brain activation, making their study in functional neuroimaging very difficult. In this respect, SPECT is probably the most appropriate procedure for the reason that the radiotracer can be simply administered during the clinical events, well before the brain images are acquired. A example of such a study pertains to sleepwalking (Bassetti et al., 2000). Finally, and not least, the theoretical framework necessary for designing the protocol of clinical neuroimaging studies is not necessarily available for all sleep disorders. For instance, the discovery of the hypocretin system and its role in narcolepsy in the late 1990s (Lin et al., 1999) has indubitably changed how experimental designs should be run in neuroimaging in narcoleptic patients. Nevertheless, alternative approaches are available, as the functional and structural consequences of these sleep disorders can also be assessed during wakefulness, as seen above.

A third area of interest is the establishment of a nosography of sleep disorders. For instance, neuroimaging could help classify different subtypes of insomnia in terms of their underlying characteristic patterns of regional brain activity, an approach that may prove complementary to the clinical observation.

Finally, functional neuroimaging can also be used to assess the effects of hypnotic drugs on regional brain function. This may enlighten our understanding of their effects, assuming that hypnotic medications inducing typical patterns of brain activation might rely on cellular mechanisms similar to those prevailing in normal sleep.

Although substantial progress in methodology has been made, a large research effort is still needed to characterize better pathophysiological mechanisms of sleep disorders, teasing apart their causes from their consequences. Optimally, brain functional imaging should be helpful in order to assess, in an individual patient, the functional and structural consequences of long-term sleep disruption.

These considerations argue for closer collaboration and partnership between basic neuroscientist sleep researchers, sleep clinicians, and neuroimagers in designing and conducting more informative (multimodal) experiments in a large number of sleep disorders.

**ACKNOWLEDGMENTS**

The authors are supported by the Fonds National de la Recherche Scientifique (FRNS) (Belgium; grant number 3.4516.05 to Martin Dressel). This work was additionally supported by the research funds of the University of Liège, the Queen Elisabeth Medical Foundation, and the Interuniversity Attraction Pole program.
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